Docket No.: 0020-4348P
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Eijiro WATANABE et al.

Application No.: 08/992,914 Confirmation No.: 4405

Filed: December 18, 1997 Art Unit: 1638

For: RAFFINOSE SYNTHASE GENES AND THEIR USE Examiner: D. H. Kruse

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

As required under § 41.37(a), this brief is filed more than two months after the Notice of Appeal filed in this case on June 1, 2006, and is in furtherance of said Notice of Appeal.

The fees required under § 41.20(b)(2) are addressed in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

I. REAL PARTY IN INTEREST

The Assignee of the present application is Sumitomo Chemical Company, Ltd. now of Tokyo, Japan.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

A Notice of Appeal was filed in the co-pending application 09/301,766 on December 22, 2006.

III. STATUS OF CLAIMS

The following is the status of the claims as of the mailing of the Final Office Action on December 1, 2005:

Claims 6, 43 and 46-86 are pending in the application.

Claims 6 and 43 are allowed. The Examiner's decision rejecting claims 46-86 has been appealed.

Claims 46-51 stand rejected under 35 U.S.C. § 101.

Claims 48-77 and 82-86 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support in the specification.

Claims 46-77 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement by the disclosure of the specification.

Claims 46, 47, 52, 53, 55 and 59-86 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-2, 16-23 and 28-30 of copending application no. 09/301,766.

IV. STATUS OF AMENDMENTS

No further amendments or arguments have been filed pursuant to the Final Office Action of December 1, 2005.

V. SUMMARY OF CLAIMED SUBJECT MATTER

In the following explanation of support for claim recitation, page and line numbers are as in the Substitute Specification filed April 14, 2000 and Sequence Listing Identifier number are as in the Substitute Sequence Listing filed July 30, 1999.

Claim 6 (allowed) is directed to an isolated nucleic acids of a recited sequence. Support for this embodiment is found, *e.g.*, in the Sequence Listing at SEQ ID NO: 1

Claim 43 (allowed) is directed to an isolated nucleic acid encoding a recited amino acid sequence. Support for this embodiment is found, *e.g.*, in the Sequence Listing at SEQ ID NO: 2.

Claims 46, 48 and 50 are directed to nucleic acids encoding polypeptides of a recited amino acid sequence. Support for these embodiments is provided, *e.g.*, in SEQ ID NOS: 4, 6 and 8, respectively.

Claims 47, 49 and 51 are dependent upon claims 46, 48 and 50, respectively, and recite particular nucleic acid sequences encoding the respective amino acid sequences. Support for these embodiments is found, *e.g.*, in the Sequence Listing in SEQ ID NOs: 3, 5 and 7, respectively.

Claim 52 is directed to an isolated nucleic acid encoding an amino acid sequence having a recited biochemical activity, the nucleotide sequence be selected from among recited SEQ ID NOs: 1, 3, 5 or 7 or encoding an amino acid from among recited SEQ ID NOS: 2, 4, 6 or 8.

Support for this embodiment is provided in the specification at, *e.g.*, the Sequence Listing SEQ ID NOs: 1-8, taken with page 3, lines 3-6.

Claims 53-58 are directed to an isolated nucleic acid encoding an amino acid sequence having a recited biochemical activity, that is obtained by nucleic acid amplification utilizing primer oligonucleotides of recited sequences upon template nucleic acids obtained from recited plant genera. Support for this embodiment as to recited primer sequences is provided by the Sequence Listing; remaining elements of the claim are described at, *e.g.* pp. 9-21 of the specification, and the working examples 1-12 at pp. 30-46.

Claims 59-62 are directed to chimeric genes comprising the isolated nucleic acids described as above, operatively linked to a promoter. This embodiment, and especially the additional promoter feature, are described in the specification at, *e.g.* page 24, lines 3-21.

Claims 65-66 are directed to plasmids comprising the isolated nucleic acids described as above. This embodiment of the invention is disclosed at, *e.g.* page 25, lines 9-15.

Claims 63, 64 and 67-72 are directed to transformants or host organisms transformed with plasmids or chimeric genes described as above. Support for these embodiments is provided at, *e.g.*, page 24, lines 22 to page 26, line 3.

Claims 73-74 are directed to methods for metabolic transformation of a plant utilizing the nucleic acids described as above. These embodiments are described in the specification at, *e.g.* page 7, lines 5-8 and also at page 26, lines 4-17.

Claims 75-86 recite a subset of the particular nucleic acids or amino acid sequences described in claims 52, 53, 59, 61, 65, 66, 73, 74 and 77, respectively, and so are supported by the specification in the manner explained above.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are to be reviewed on appeal:

Claims 46-51 are rejected under 35 U.S.C. § 101, for alleged lack of support by either a substantial asserted utility or by a well-established utility. (As stated in paragraph 4 of the Final Office Action.)

Claims 48-77 and 82-86 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description of the claimed invention. (As stated in paragraph 5 of the Final Office Action.)

Claims 46-86 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable an isolated nucleic acid of SEQ ID NO: 4, 6 or 8, nor an isolated nucleic acid isolated from any leguminous, lamiaceous or monocotyledonous plant. (As stated in paragraph 6 of the Final Office Action.)

VII. ARGUMENT

VIIA. Rejection Under 35 U.S.C. § 101

Claims 46-51 stand rejected under 35 U.S.C. § 101, for alleged lack of utility. Applicants submit that the Examiner's decision is incorrect, and respectfully request that the Board reverse the Examiner's decision.

The Examiner asserts that the present specification does not allege a substantial utility for the claimed isolated nucleic acids, or alternatively, that no substantial utility for the claimed nucleic acids is known to one of ordinary skill in the art.

A "substantial" utility is one that is a "real world" utility, *i.e.* a use to which the invention would actually be applied by one of ordinary skill in the art. The present specification expressly describes that the present invention related to isolated nucleic acids encoding raffinose synthase enzymes (see, page 2, lines 18-20). The specification describes raffinose synthase enzymes as catalyzing the rate-limiting step in raffinose oligosaccharides, which oligosaccharides are important in the food value of plants. The specification explains that raffinose synthases are present in plants of widely divergent species and urges that manipulation of the raffinose content of a plant, by manipulation of the amount of raffinose synthase expressed in the plant, is useful for making plants more healthy as foods. See, pages 1-2 of the specification. The specification also alleges that this manipulation can be in the form of over-expression of a raffinose synthase enzyme, or by decreasing the expression of raffinose synthase using antisense technology or the like. See, page 26, lines 4-17.

The Examiner does not at all challenge this asserted utility of the invention. Thus, it must be accepted that the asserted utility of the invention is credible, substantial and specific. Such is consistent with the present allowance of claims 3 and 46.

Rather, the Examiner takes a position that, because there exists a superfamily of proteins in plants that encompasses stachyose synthases (STSs) in addition to the raffinose synthases (RFSs) of the invention, the asserted utility of the presently claimed nucleic acids is not established for any amino acid sequence, and so for the nucleic acid encoding it, for which an actual demonstration of raffinose synthase activity has not yet been made. The Examiner asserts that the degree of sequence identity among the STSs and among the RFSs is sufficiently low that one kind of enzyme is not distinguishable from the other kind of enzyme merely on the basis of the amino acid sequence encoded by the nucleic acid that is the subject matter of the present claims. The Examiner asserts that the Applicant has not specified a structure-function relationship sufficient to identify the genus of the nucleic acids of the invention.

Applicants submit that the Examiner's position is incorrect and that the present record contains sufficient **evidence** that one of ordinary skill in the art is able to distinguish a RFS from

a STS by analysis of the overall degree of amino acid sequence similarity of any desired protein to the amino acid sequence of one of the SEQ ID NOs: 2, 4, 6 or 8 of the present application.

The present claims 46-51 recite defined amino acid sequences or specific nucleotide sequences that are one sequence that may encode the defined amino acid sequence. The nucleic acid sequences are those of the raffinose synthase cDNAs cloned from soybean, Japanese Artichoke and corn, as in Examples 7, 9 and 11 of the specification; the amino acid sequences are those obtained by translation of the cDNA sequences.

As to the "structure-function relationship" defining the genus of the nucleic acids encoding a raffinose synthase, Applicants do not see how this applies to the present claims 46-51. As explained above, a distinct structure of a particular amino acid sequence or of a particular nucleic acid sequence is recited in these claims. The present specification, and the record of the present application, makes clear that the question of utility before the Board relates to whether the amino acid sequence of a particular protein is sufficient for determining whether or not the protein would be more likely than not to possess raffinose synthase activity.

There is substantial evidence of record that one of ordinary skill in the art can distinguish a RFS enzyme from a STS enzyme solely on the basis of amino acid sequence. Applicants have previously provided phylogenetic analyses of the amino acid sequence of RFSs and STSs and have established that the degree of sequence homology among RFSs and among STSs is significantly higher than the degree of homology between RFSs and STSs. This relationship is robust to analysis using two different sequence identity determination algorithms. See, Table 3 attached to the Amendment filed November 15, 2004 and Table 2 attached to the Amendment filed February 25, 2004, both presented in Evidence Appendix B. To this evidence, Appellants have added the Declaration of Mr. Akitsu Nagasawa also provided in Evidence Appendix B. Mr. Nagasawa attests to the methodology used to generate the data in Tables 2 and 3 and presents an additional analysis using yet a third approach to calculating sequence identity.

Mr. Nagasawa's Declaration shows that distinction among RFSs, STSs and Seed Imbibition Proteins (SIPs) solely upon amino acid sequence data is possible using any of three

commonly used sequence homology determination algorithms; CLUSTAL, BLAST (as tBLASTn or BLASTp) and BLAST 2 SEQUENCES. Thus, the ability to distinguish RFSs from STSs (and SIPs) based upon sequence data is robust to the particular analysis program used. Furthermore, the phylogenetic tree generated from the sequence homology analyses shows a deep division between RFSs and STSs, demonstrating that these two kinds of enzymes are readily distinguishable families based only upon amino acid sequence data.

Accordingly, and as testified by Mr. Nagasawa, the identity of a protein as a raffinose synthase is readily established by analysis of its sequence in comparison to the sequences shown in the present sequences listing, especially by comparison to SEQ ID NO: 2, the identity of which as a raffinose synthase the Examiner does not challenge. The Board should also note that the conclusion reached by Mr. Nagasawa is consistent with the text of the specification at page 23, lines 14-17.

The Examiner asserts that, at the time the present application was filed, the state of the art was such that only one gene encoding a raffinose synthase protein was known in the art, being from cucumber and disclosed in U.S. Patent 6,166,292. (See, page 3 of the December 1, 2005, Office Action.) Therefore, there was no feasible basis for comparing proteins of the present invention to "raffinose synthases" and conclude the protein of a similar sequence would have raffinose synthase activity.

This argument of the Examiner is not persuasive, not the least because it ignores that the present specification includes a second amino acid sequence, SEQ ID NO: 2, demonstrated to exhibit raffinose synthase activity and three additional sequences that are compared to that sequence. Appellants' argument is that the sequences independently described by the specification are identifiable as a group separate from sequences that form another group of sequences, which happen to be stachyose synthases (or from a second group of SIPs, see the Declaration of Mr. Nagasawa).

The Examiner should not substitute his own bare opinion for the testimony of one of ordinary skill in the art, at least not in the absence of **evidence** to support such substitution. Appellants submit that this represents legal error sufficient to reverse the Examiner's decision.

Furthermore, given the amino acid sequence, and identification of any particular protein as a raffinose synthase by virtue of homology to SEQ ID NO:2 (and 4, 6 and 8), the hypothesis of raffinose synthase activity can be confirmed by the assay for raffinose synthase activity described in the present specification (at page 27, lines 21-23), by reference to Lehle and Tanner, *Eur. J. Biochem.* 38:103-110 (1973); a copy of this paper is provided as a part of the Evidence Appendix B. It can hardly be said that testing of a protein for activity using a disclosed assay method is undue experimentation. One of ordinary skill in the art can readily determine if in fact any one protein having a defined amino acid sequence has the activity of combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule that defines a raffinose synthase enzyme.

The Board is gently reminded that Appellants' burden of proof on this issue is merely the preponderance of the evidence. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Appellants submit that the Nagasawa Declaration, the Exhibit 1 and Tables 2 and 3 of record, and the text of the specification establish by a preponderance over any evidence submitted by the Examiner that the invention as claimed in claims 46-51 has a substantial utility. Appellants accordingly assert that the utility of the invention as described by claims 46-51 is well described in the specification, or alternatively is well established in the art, and accordingly the Examiner's decision to maintain the instant rejection should be reversed.

VIIB. Rejections Under 35 U.S.C. § 112, first paragraph - written description

VIIB.1. Claims 48-51

Claims 48-77 and 82-86 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support of the claimed invention. Appellants respectfully submit that this rejection should be reversed.

The Examiner takes a position that, despite the recitation in many of the claims of structural features defining the genus of the enzymes claimed, and in some instances a further limitation of the claims to the operative embodiments of those enzymes having a recited biochemical activity,

> Applicant has failed to establish a relationship between the structure of the claimed nucleic acids and the function of the encoded protein. In addition, description of a partial coding sequence does not adequately describe a nucleic acid encoding a raffinose synthase as asserted by Applicant."
> The Examiner further states that,

> [I]t cannot be held that DNA molecules claimed in [the] application have been described, since applicants' contention that they were in physical possession of protein does not establish their knowledge of that protein's amino acid sequence or any of its other descriptive properties, even though the amino acid sequence is [an] inherent property of [the] protein, and since [the] application does not provide adequate functional description, in that, with only partial amino acid sequence disclosed, chemical structure of nucleic acid molecules that can serve function of encoding protein's amino acid sequence cannot be determined.

See, the Office Action of March 11, 2005, at page 5.

With respect to claims 48-51, such stated grounds for this rejection are nonsense, and furthermore underscore the summary nature of the rejection.

There are no "bright line" tests for whether or not a specification provides adequate written description of a claimed invention. The Examiner must carefully review the claims, and carefully review the specification to determine whether, in view of what is known in the art at the time the application was filed, the specification provides evidence that the inventor was in "possession" of the invention as claimed. *Capon v. Eshhar,* 76 USPQ2d 1078 (Fed. Cir. 2005); *Faulkner v. Inglis,* 79 USPQ2d 1001 (Fed. Cir. 2006).

Appellants note that claims 48-51 recite specific amino acid sequences to be encoded by the claimed nucleic acid, or a specific nucleotide sequence *per se*. Accordingly, it cannot be said that these claims do not describe the structural features of the claimed invention.

Furthermore, the Examiner's premise that only partial amino acid sequences are provided is incorrect, at least as to SEQ ID NOs: 1-4. As to SEQ ID NOs: 5-8, Appellants note that the claims are directed to nucleic acids "comprising" the sequences 5 and 7, encoding the partial RFS proteins of SEQ ID NOs: 6 and 8. Nonetheless, these sequences must be taken as described to this extent.

The working Examples 5-11 of the specification provide description of the experiments in which the cDNAs encoding raffinose synthases from broad bean, soybean, Japanese artichoke and corn are obtained. The experiments of Examples 5-9 are described in a manner that indicates that the full-length cDNA is cloned, and thus the coding portion from amino terminal to carboxy-terminal of the raffinose synthase protein is obtained. See, *e.g.* Example 6 at page 32, in which use of data from the 5' end of a first cDNA clone are used to construct a primer for extending the cDNA at least to the end of the coding portion of the corresponding mRNA. The amino acid sequence set forth in SEQ ID NO: 4 is complete, and SEQ ID NOs: 6 and 8 are partial protein sequences, but sufficiently long to allow determination that they encode a RFS, or at least part of one, by their degree of overall identity to the known RFS of SEQ ID NO: 2.

The Examiner has allowed claims 6 and 43, directed to a nucleic acid of SEQ ID NO: 1, and to a nucleic acid encoding the amino acid sequence of SEQ ID NO: 2. The protein of SEQ ID NO: 2 is the raffinose synthase from broad bean, which was purified as described in Example 3, and the activity of which was proven in Example 4. The amino-terminal amino acid sequence of the purified protein was obtained, and this information was used for cloning the cDNA having the sequence of SEQ ID NO: 1, encoding the amino acid sequence of SEQ ID NO: 2 (Examples 5 and 6). The activity of the cloned cDNA as encoding a raffinose synthase was established by expressing the cloned cDNA in *E. coli* and detection of raffinose synthase activity in a lysate of the transformed bacteria (Example 8).

In Example 9 the amino acid sequence data from SEQ ID NO: 2, *i.e.* the amino acid sequence of a protein established to have raffinose synthase activity, are used to make PCR primers that are used to isolate full-length cDNAs encoding raffinose synthases from soybean.

In Example 10 and 11, the data are used to make primers for obtaining additional cDNAs from Japanese artichoke and corn. The resulting cDNAs are translated, and the resulting amino acid sequences are compared to the full-length amino acid sequence of SEQ ID NO: 2. From this analysis, the Appellants conclude that SEQ ID NOs: 4, 6 and 8 represent the amino acid sequence of raffinose synthases from these species.

Appellants burden is to establish, by a preponderance of the evidence, that the amino acid sequences of SEQ ID NOs: 4, 6 and 8 represent proteins having raffinose synthase activity. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The particular amino acid sequences in question were obtained by a cloning method generally accepted in the art as useful for cloning functionally homologous proteins across species lines. Comparison of the full-length of these sequences against SEQ ID NO: 2, known to encode a raffinose synthase, shows that they have a degree of sequence identity accepted by one of ordinary skill in the art to establish that they are likely to be raffinose synthase enzymes, as opposed to stachyose synthases or seed imbibition proteins. This conclusion is supported by the Declaration testimony of Mr. Nagasawa and furthermore, Mr. Nagasawa's method of analysis has been shown to be robust to the application of three different computational methods. Against this evidence, the Examiner has raised only his opinion supported by an analysis that is incomplete. Accordingly, Appellants submit that they have met their burden of proof on this issue.

The particular clones of SEQ ID NOs: 3, 5 and 7, encoding amino acid sequences 4, 6 and 8, are described as being obtained in working examples of the specification and specific data resulting from those experiments are provided in the specification. Thus, there can be no dispute that Appellants are in physical possession of the subject matter claimed in claims 48-51.

Thus, the instant rejection of at least claims 48-51 under 35 U.S.C. § 112, first paragraph, for failure of the specification to provide adequate written description of the claimed subject matter, must be reversed.

VIIB.2. - claim 52

Compared to claims 48-51, claim 52 recites a further feature that the protein encoded by the claimed nucleic acid has the biochemical activity of raffinose synthase (described as the chemical reaction catalyzed). To the degree that there is any doubt that proteins of SEQ ID NOs: 4, 6 or 8 might lack raffinose synthase activity, they would be excluded from the scope of claim 52 by this feature. Claim 52 thus obviates the Examiner's concern that mere computational analysis of amino acid sequence data is inadequate to establish biochemical activity and so the rejection of claim 52 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support by the specification, may be reversed for this additional reason.

VIIB.3. - claims 53-58

Claims 53-58 are directed to an isolated nucleic acid encoding an amino acid sequence of a protein that exhibits the biochemical activity of raffinose synthase (described as the chemical reaction catalyzed). The nucleic acids are described in product-by-process terms as being obtained by amplification using particularly recited primers and template nucleic acids obtained from particular families of plants. The end product nucleic acid is one that hybridizes with a defined nucleic acid of SEQ ID NO:1, 3, 5 or 7, depending upon which genus of plant the product from which the product is obtained, the genus of the plant being the same as the genus of plant from which SEQ ID NO: 1, 3, 5 or 7 is obtained.

It is entirely proper to claim an invention in product-by-process terms. *Fiers v. Revel*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Claims 53-58 in effect describes the working examples of the specification, which represent an actual reduction to practice of four different species of the invention. Therefore, it must be accepted that the process described in claims 53-58 is effective for obtaining operable embodiments of the invention.

Furthermore, contrary to the Examiner's assertion that the claims do not include any correlation between structure and function, the claims include two structural features that are connected to operable embodiments. First, there are the primer sequences utilized in the process.

These primers represent portions of the raffinose synthase cDNAs of the family of plant recited that are conserved among the raffinose synthases from that family, as evidenced by their successful use in isolating cDNAs encoding raffinose synthases from plants of those families. The primer sequences are incorporated into the product nucleic acid, and so represent at least a minimal specific sequence in the product. Second, the claims recite that the nucleic acid obtained as the amplification product must hybridize to a nucleic acid that is known to encode a raffinose synthase[1] under conditions accepted in the art to constrain the hyrbridizing sequence to those having a high degree of sequence identity.

As explained above, claims 53-58 describe embodiments obtained using the working examples 5-11 of the specification. Thus, there can be no doubt that Appellants are in "possession" of several embodiments of the invention within the scope of claims 53-58.

Because claims 53-58 include structural features correlated with function of the obtained nucleic acid as a raffinose synthase, and because the working examples of the specification demonstrate actual reduction to practice of the invention as set forth in claims 53-58, Appellants submit that these claims are well-supported by the specification. Accordingly, the rejection of claims 53-58 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support in the specification, should be reversed.

VIIB.4. - claims 59-62

Claims 59-62 relate to chimeric genes comprising the isolated nucleic acids described in claims 6, 43, and 46-53, operatively linked to a promoter. The Examiner has not set forth any particular explanation of any separate grounds of rejection other than those explained above, and therefore the various arguments applied to claims 46-51, 52 or 53-58, as may be applicable, should be applied to these claims as well. The Board should consider that the promoter aspect of

[1]In the case of SEQ ID NO:2, this is established by assay of the enzyme encoded by the nucleic acid. In the case of SEQ ID NOs:4, 6 and 8, this is established by a degree of sequence identity that separates raffinose synthase genes from genes encoding related enzymes

claims 59-62 is thus deemed well-described by the specification and the instant rejection should be reversed as to claims 59-62.

VIIB.5. - claims 65- 66

Claims 65 and 66 relate to plasmids comprising the isolated nucleic acids described in claims 3, 46 and 48-53. The Examiner has not set forth any particular explanation of any separate grounds of rejection other than those explained above, and therefore the various arguments applied to claims 46-51, 52 or 53, as may be applicable, should be applied to these claims as well. The Board should consider that the plasmid aspect of claims 65 and 66 is thus deemed well-described by the specification and the instant rejection should be reversed as to claims 65 and 66.

VIIB.6. - claims 63, 64 and 67-72

Claims 63, 64 and 67-72 relate to transformants and host organisms transformed with chimeric genes or plasmids described in claims 59-63 or 65-66. The Examiner has not set forth any particular explanation of any separate grounds of rejection other than those explained above, and therefore the various arguments applied to claims 46-51, 52, and 53-58, as may be applicable, should be applied to these claims as well. The Board should consider that the transformant and host organism aspects of claims 63, 64 and 67-72 are thus deemed well-described by the specification and the instant rejection should be reversed as to claims 63, 64 and 67-72.

VIIB.7. - claim 73

Claim 73 is directed to a method for metabolic modification of a plant using the cloned DNA described in claim 52. The Examiner has not set forth any particular explanation of any separate grounds of rejection other than those explained above, and therefore the arguments applied to claim 52, should be applied to this claim as well. The Board should consider that the

metabolic transformation aspect of claim 73 is thus deemed well-described by the specification and the instant rejection should be reversed as to claim 73.

VIIB.8. - claim 74

Claim 74 is directed to a method for metabolic modification of a plant using the cloned DNA described in claim 53. The Examiner has not set forth any particular explanation of any separate grounds of rejection other than those explained above, and therefore the arguments applied to claim 53, should be applied to this claim as well. The Board should consider that the metabolic transformation aspect of claim 74 is thus deemed well-described by the specification and the instant rejection should be reversed as to claim 74.

VIIB.9. - claims 75-76

Claim 75 claims a nucleic acid that encodes an amino acid sequence that is one of SEQ ID NOs: 2, 4, 6 or 8, or the complement of one of these sequences. Claim 76 claims the nucleic acid sequence of SEQ ID NOs: 1, 3, 5 or 7, or the complement thereof. SEQ ID NOs: 1-8 are specifically set forth in the specification. Any nucleic acid that encodes any amino acid sequence is readily derived by one of ordinary skill in the art from the amino acid sequence. The complement of any given nucleotide sequence is immediately apparent to one of ordinary skill in the art. Accordingly, there can be no doubt that the subject matter of claims 75 and 76 is well-described in the application and the rejection of claims 75 and 76 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description in the specification must be reversed.

VIIB.10. - claim 77

Claim 77 represents a subgenus compared to claim 53, in that the plant from which the template nucleic acid is obtained is more specifically defined to the level of a species. Compared to claim 53, claim 77 more closely describes the working examples 5-11, and so to that degree must be acknowledged to be well-described by the specification. Thus, the instant rejection should be reversed as to claim 77.

VIIB.11. - claims 78-81

Claims 78-81 represent a subset of the scope of claims 52, 59, 65 and 73, and recite the particular sequences of SEQ ID NO: 1 or 2, demonstrated to represent a protein having raffinose synthase activity or to encode a such a protein, and to SEQ ID NO: 4 which has a higher degree of sequence identity to SEQ ID NO: 2 compared to SEQ ID NOs: 6 and 8, and to SEQ ID NO: 3, encoding the amino acid sequence of SEQ ID NO: 4. The rationale of the Examiner in maintaining the present rejection relates to the ability of one of ordinary skill in the art to distinguish a RFS-encoding nucleic acid from a nucleic acid encoding a STS or SIP. SEQ ID NO: 2 and SEQ ID NO: 4 are 75% identical overall. (See, the Declaration of Mr. Nagasawa and the Sequence Listing; SEQ ID NO: 4 is a sequence of 781 amino acids, SEQ ID NO: 2 is a sequence of 799 amino acids.) Appellants submit that the relatively high degree of identity between SEQ ID NOs: 2 and 4 very clearly establishes that SEQ ID NO: 3 encodes a RFS protein, rather than a STS or SIP, and accordingly the subject matter of claims 78-81 must be deemed well-described by the present specification. Furthermore, these sequences are those encoded by the full-length clones described in the specification, which are demonstrated to or as explained above very likely to provide an active enzyme. Therefore, the instant rejection must be reversed as to claims 78-81.

VIIB.12. - claims 84-85

Claims 84 and 85 are directed to embodiments falling within claims 66 and 74, respectively. Claims 84 and 85 recite the nucleic acid used in the claimed plasmid and method for metabolic transformation in product-by-process terms. The particular primers described in these claims, when used in the working examples, resulted in cloning of the nucleic acid of SEQ ID NO: 1, encoding a protein having the amino acid sequence of SEQ ID NO: 2 and demonstrated to have raffinose synthase activity, and the nucleic acid of SEQ ID NO: 3, which encodes a protein (SEQ ID NO: 4) having a higher degree of sequence identity to SEQ ID NO: 2 compared to SEQ ID NOs: 6 and 8. The rationale of the Examiner in maintaining the present rejection relates to the ability of one of ordinary skill in the art to distinguish a RFS-encoding

nucleic acid from a nucleic acid encoding a STS or SIP. SEQ ID NO: 2 and SEQ ID NO: 4 are 75% identical overall. (See, the Declaration of Mr. Nagasawa and the Sequence Listing; SEQ ID NO: 4 is a sequence of 781 amino acids, SEQ ID NO: 2 is a sequence of 799 amino acids.) Appellants submit that the relatively high degree of identity between SEQ ID NOs: 2 and 4 very clearly establishes that SEQ ID NO: 3 encodes a RFS protein, rather than a STS or SIP. Furthermore, these are the sequences that are "full-length" and demonstrated to or thus very likely to represent an active enzyme (or encode one). Accordingly the subject matter of claims 84 and 85 must be deemed well-described by the present specification. Therefore, the instant rejection must be reversed as to claims 84-85.

VIIB.13. - claim 86

Claim 86 describes a subset of the nucleic acids otherwise described in claim 77. Claim 86 describes the claimed nucleic acid in product-by-process terms. The particular primers described in claim 86, when used in the working examples, resulted in cloning of the nucleic acids of SEQ ID NO: 1, demonstrated to encode a protein having raffinose synthase activity (SEQ ID NO: 2), and SEQ ID NO: 3, which encodes a protein having the amino acid sequence of SEQ ID NO: 4 that has a higher degree of sequence identity to SEQ ID NO: 2 compared to SEQ ID NOs: 6 and 8. The rationale of the Examiner in maintaining the present rejection relates to the ability of one of ordinary skill in the art to distinguish a RFS-encoding nucleic acid from a nucleic acid encoding a STS or SIP. SEQ ID NO: 1 and SEQ ID NO: 4 are 75% identical overall. (See, the Declaration of Mr. Nagasawa and the Sequence Listing; SEQ ID NO: 4 is a sequence of 781 amino acids, SEQ ID NO: 2 is a sequence of 799 amino acids.) Appellants submit that the relatively high degree of identity between SEQ ID NOs: 2 and 4 very clearly establishes that SEQ ID NO: 3 encodes a RFS protein, rather than a STS or SIP. Furthermore, these are the sequences that are "full-length" and are either demonstrated to or very likely to represent an active enzyme (or encode one). Accordingly the subject matter of claim 86 must be deemed well-described by the present specification. Therefore, the instant rejection must be reversed as to claim 86.

VIIC. 35 U.S.C. § 112, first paragraph - Enablement

Claims 46-86 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of the claimed invention by the disclosure of the specification. The Examiner's position on this issue is essentially that grouping of enzyme primary structures into families based upon sequence identity is insufficient to support an assertion that a protein of unconfirmed activity will have the activity ascribed to that family demonstrated by biochemical assay of at least one of its members. The Examiner therefore asserts that the present specification is enabling of "how to use the invention" only for those proteins for which activity as a raffinose synthase is actually demonstrated by biochemical assay. In the present instance, the Examiner asserts that the claims must be limited with respect to the amino acid sequence of the enzyme to SEQ ID NO: 2, which is the sole amino acid sequence for which actual raffinose synthase activity has been described in the present specification.[2]

Appellants disagree.

VIIC.1. Claims 46-58 and 75-77

The question of enablement is to be considered under a multifactor analysis as set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). It is incumbent upon the Examiner to first establish a *prima facie* case for lack of enablement. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (holding examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). Should the Examiner do so, then the Appellant must establish, by the preponderance of the evidence, that no undue experimentation is required to practice the invention as claimed. *In re Oetiker*, 24 USPQ2d at 1444.

[2]It is only the breadth of the claims with respect to sequence of the nucleic acid that the Examiner has challenged during prosecution to date. The Examiner thus has accepted enablement of elements of the claims related to construction of plasmids, the making of transformants, and use of the cloned nucleic acids to effect metabolic modification of host organisms. Sufficiency of neither enablement nor of written description of these aspects of the claims is before the Board for review.

Appellants first submit that the Examiner has never established a proper *prima facie* case for lack of enablement of the claimed invention. As explained in the Remarks of Appellants' paper of November 15, 2004, proper analysis of the question of enablement requires that the factors of 1) the breadth of the claims, 2) the nature of the invention, 3) the level of ordinary skill in the art, 4) the amount of experimentation needed, 5) the state of the art at the time the invention was made, 6) the amount and quality of guidance provided by the specification, 7) the presence or absence of working examples and 8) the predictability in the art. Despite the Examiner's protestation to the contrary (see, the Office Action of March 11, 2005, at page 6), the Examiner has only addressed the predictability in the art, in the sense that his position is that, because the specification only actually demonstrates biological activity as a raffinose synthase for SEQ ID NO: 2, and the degree of sequence identity among the amino acid sequences identified in the working examples is as low as 60%, Appellants cannot reliably assign the biochemical activity of a raffinose synthase to the amino acid sequences of SEQ ID NOs:4, 6 and 8. To the degree that the Examiner has addressed the other factors to be considered at all, it is only to describe his disagreement with positions on these issues expressed by Appellants. Such reverses the correct procedure for determining enablement and is an improper approach to making a rejection for lack thereof.

Despite the failure of the Examiner to first establish a proper *prima facie* lack of enablement, Appellants have provided their own analysis of the *Wands* factors in the Remarks portion of their paper filed November 15, 2004. These remarks are reproduced here for convenient review by the Board:

> Rejection for alleged lack of enablement
>
> Claims 1, 4, 7, 9, 11-13, 15-18, 30-36, 40, 41 and 44 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement by the specification. These claims have been canceled, rendering this rejection moot. Applicants submit that this rejection should not be applied to the present claims.
>
> Applicants note first that analysis of enablement is a question of whether "undue experimentation" is required to practice the invention throughout its claim scope. Consideration of the question of undue experimentation is by weighing of

each of several factors enumerated in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The Examiner fails to meet his burden of establishing a *prima facie* lack of enablement. The Examiner's analysis of the question of undue experimentation looks only at the factor of whether working examples of the claimed invention are described in the specification and an assertion that it is unpredictable whether any particular nucleic acid produced according to the teachings of the invention would in fact exhibit raffinose synthase activity. This analysis is legally insufficient to establish *prima facie* lack of enablement, as the Examiner fails to consider the breadth of the claims, the nature of the invention, the level of ordinary skill in the art, the quantity of the experimentation needed, the guidance provided by the specification (other than the presence or absence of working examples) and the state of the art at the time the invention was made. Furthermore, the kind of predictability, *a priori* knowledge of functionality of the enzyme obtained using the methods of the invention, is not the kind of predictability envisioned by the Court in *Wands*. The instant rejection cannot properly be sustained against any claims.

The nature of the invention and the breadth of the claims

The claimed invention relates to isolated nucleic acids that encode an enzyme having a defined biological activity. The claims recite that the invention lies in a nucleic acid that is defined by inclusion of at least certain sequence features, hybridizes to a certain reference sequence and encodes a protein having a defined enzymatic activity.

The art of molecular biology, in particular the art of expression of recombinant proteins, is one in which the artisan of ordinary skill expects to perform a few weeks or months of experimentation in generating variants of a protein, then isolating clones encoding those variants and then (perhaps) re-cloning the isolated variants into vectors for expressing a protein, and then screening expressed proteins for activity.

The level of ordinary skill in the art

The artisan of ordinary skill in the art of cloning and expressing recombinant proteins is generally accepted as one having a Ph.D. degree and perhaps higher. Such a person is skilled in the design and performing of experiments for isolating DNA clones and for screening them for a desired property, for example encoding a protein having a particular activity.

The amount of experimentation needed

The amount of experimentation needed to practice the present invention is not unduly large or burdensome. The practitioner must isolate a template genomic DNA from an organism, perform a polymerase chain reaction using primers described in the specification to generate an amplified fragment, clone that fragment into an expression vector, express the encoded protein and then screen the protein for activity as a raffinose synthase. All of these steps are either well-known in the art or described in detail in the specification and furthermore are expected to be performed by the artisan of ordinary skill.

The state of the art at the time the invention was made

At the time the invention was made, the state of the art of molecular biology was such that the various laboratory operations that must be performed to carry out the experimentation required to practice the instant invention, *i.e.* cloning of DNA molecules and expressing them in a host cell, were routine. Also, polymerase chain reaction amplification of nucleic acids was routine.

The raffinose content of a number of organisms, especially including plants and some algae, was known. The biochemistry of raffinose synthesis in plants had been established, and the role of raffinose synthases as rate-limiting of raffinose production was known.

A biochemical assay for raffinose synthase activity was described. See Exhibit 4 attached, Lehle et al., *Eur. J. Biochem.* 38:103 (1973).

The guidance provided by the specification including the presence or absence of working examples

The specification provides ample guidance to the skilled artisan for practicing the invention broadly. In particular, the specification discloses in detail how to clone DNAs encoding putative raffinose synthase enzymes. The specification provides details such as organisms likely to be useful for isolating template genomic DNA or cDNA (see, *e.g.* page 1, lines 9-14) and methods for cloning DNA encoding a putative raffinose synthase enzyme from an RNA fraction, including an extensive list of primers that can be utilized for PCR amplification from templates obtained from different organisms (see, *e.g.* page 10, line 11 to page 18, line 14). The specification describes methods for expressing the cloned DNA in plant cells and in bacteria (see, *e.g.* page 24, line 3 to page 27, line 23) and an example of expression in bacteria (Example 8 beginning at page 39). The specification describes how to purify raffinose synthase from plant cells (see, *e.g.* Example 3 beginning on page 32). The specification describes a

biochemical assay for raffinose synthase, referring to the Lehle article noted above and summarizing the procedure in Example 2 beginning at page 31.

The specification also provides a number of working examples of isolation of partial or complete raffinose synthase genes from a number of different plants. See, Examples 7 and 9 to 11) and of transformation of a plant (soybean) with a cloned DNA encoding a raffinose synthase (Example 13).

The predictability in the art

The Examiner asserts that the art of recombinant DNA cloning and recombinant protein expression is unpredictable. The Examiner argues that a practitioner of the invention must engage in trial and error experimentation to identify cloned DNAs that encode functional raffinose synthase genes.

The Examiner's argument is simply incorrect. First, the skilled artisan can follow detailed teachings in the specification of how to clone, express and evaluate DNAs that are likely to encode functional raffinose synthase enzymes. It is true that it is unpredictable whether any individual clone made in an experiment will include a DNA encoding a functional enzyme, but it is not unpredictable whether the skilled artisan would succeed in identifying at least one functional DNA in an experiment as a whole. To the contrary, it is very likely that the skilled artisan would find a cloned DNA encoding a functional enzyme by following the teachings of the specification.

The Examiner is urged to read the *Wands* case in detail. In that case, an invention related to isolation of hybridomas that secreted a particular antibody was deemed broadly enabled despite that extensive screening of many cloned cell lines was necessary AND that the success rate of the screening was only 2.8%, including experiments that failed to generate any operable clones at all. The *Wands* panel expressly stated that experimentation, such as the cloning and screening experiments described in the present application, that is expected to be performed by the artisan of ordinary skill, is not undue experimentation.

Applicants submit that a proper weighing of the *Wands* factors will lead the Examiner to a proper conclusion that no undue experimentation is required to practice the present invention broadly. Accordingly, the instant rejection should not be applied against the present claims.

Furthermore, Appellants have provided evidence to support an assertion that one of ordinary skill in the art can readily distinguish a RFS from a STS or a SIP. The Nagasawa Declaration demonstrates unequivocally that the RFS subfamily of glycoside hydrolases (see

Appellants' discussion of Peterbauer et al., below) is easily distinguished from the STS or SIP subfamilies of glycoside hydrolases on the basis that RFSs are more similar to each other, and STSs are more similar to each other, than RFSs are similar to STSs. This relationship among their amino acid sequences can be used to construct a "molecular phylogenetic tree" upon a branch of which any particular amino acid sequence thought to represent a RFS or STS (or SIP) can be placed. The Nagasawa Declaration further explains that this analysis is robust in its conclusions (though perhaps the specific degrees of sequence similarity may vary) to three different approaches to sequence similarity analysis.

The Examiner has attempted to support his position regarding unpredictability in the art with evidence from the scientific literature. The Examiner has cited Richmond et al. *Plant Physiology* (2000), Duggleby, *Gene* (1997) and Peterbauer et al., *Planta* (2002). See, the Office Action of December 1, 2005, at page 9.

The Examiner asserts that Richmond et al. indicates that more than sequence similarity is needed as evidence of function, pointing out the paragraph bridging the left and right columns of page 497. Appellants see here only a description of domains present in members of the cellulose synthase family of proteins. Indeed, Richmond might be interpreted as more supportive of Appellants' position that sequence similarity is a useful tool for grouping proteins by activity. The Board might take note of Figure 1 of the paper, showing assignment of members of the family to subfamilies CesA, CesB, CesD, etc. based upon a molecular phylogeny. The Board may usefully compare Figure 1 of Richmond with Figure 1 attached to the Nagasawa Declaration, which shows a similar molecular phylogeny among RFSs, STSs and a SIP, with the result of clear separation of the three groups of enzymes.

The Examiner does not point out any particular disclosure of Duggleby. This paper describes study of the small subunit of the acetolactate synthase (ALS) from a bacterium, yeast and an alga. The paper provides an alignment of the genes from these three organisms (Figure 2). The authors note that there is only "limited similarity" among the three sequences, but nonetheless were able to detect a number of known bacterial ALS genes and also discovered the

eukaryotic versions of the gene using a BLAST search of GENBANK and the bacterial sequence (*B. flavum*) as a query. See, p. 247, under Results and Discussion. Thus, Duggleby in fact also supports Appellants' assertion that comparison of sequence data is a common technique in the art for predicting biochemical function of a protein. ("These results clearly indicate that *S. cerevisiae* and *P. purpurea* contain a gene that could encode an ALS small subunit.", at the top of the right column on p. 247.)

Peterbauer describes isolation of a raffinose synthase gene from *P. sativum* (pea). The Examiner asserts that Peterbauer teaches that RFSs, STSs and SIPs demonstrate high overall sequence homology. This has not been disputed by Appellants. Peterbauer discusses this result in terms of assignment of all three of these enzyme types to the glycoside hydrolase enzyme family. Appellants argument is that RFSs are more alike, and STSs are more alike, than RFSs resemble STSs and therefore these members of the glycoside hydrolase family are distinguishable subfamilies.

Appellants note that the Examiner has read Peterbauer rather selectively. At the top of the right column on p. 841, Peterbauer easily distinguishes a STS transcript from a RFS transcript on the basis of sequence identity.

In fact, Peterbauer uses an approach to cloning the pea RFS gene that is similar to that described in the present specification. That is, PCR primers designed from the amino acid sequence of the RFS were used to amplify template DNA from the pea plant. Then the resulting cDNA was expressed in a cell and the protein so produced was assayed for RFS activity. These teachings may usefully be compared with the working examples 2-8 of the present specification.

Peterbauer does indeed note that, "to distinguish between raffinose synthase and stachyose synthase, the primers were chosen to encompass a block of about 80 amino acids, which is exclusively present in stachyoses synthases." This does not particularly support the Examiner's position however. First, this amounts to an admission that there are amino acid sequence elements that serve to distinguish a RFS from a STS. Second, the Examiner has again quoted the paper very selectively. The portion quoted by the Examiner merely goes to a part of

the method Peterbauer used to sort among the clones obtained in a first screening. Appellants note the text at the top of the right column of p. 841, "To isolate a cDNA encoding for raffinose synthase by reverse transcription-PCR, degenerate primers were designed based upon amino acid motifs conserved among *Cucumis sativa* raffinose synthase, stachyose synthase and related sequences." Thus, Peterbauer et al. were satisfied that they could reliably distinguish among such sequences either by biochemical or sequence analysis methods.

Thus, none of the papers proffered by the Examiner in rebuttal of Appellants arguments is effective to undermine either their argument that the specification is enabling of practice of the invention, or the evidence of the Nagasawa Declaration that one of ordinary skill in the art can readily determine by amino acid sequence analysis whether a given amino acid sequence represents a RFS, a STS or a SIP.

Since the Examiner has in the first instance failed to establish a *prima facie* lack of enablement of the claimed invention, and in the second instance has failed to effectively rebut Appellants' arguments and evidence offered in support of enablement of the claimed invention, the present rejection of claims 46-58 and 75-77 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, must be reversed.

VIIC.2. - claims 59-62

Claims 59-62 relate to chimeric genes comprising the isolated nucleic acids described in claims 6, 43 and 48-53, operatively linked to a promoter. The Examiner has not set forth any particular explanation of any separate reason for lack of enablement other than those explained above, and therefore the various arguments applied to claims 46-53, as may be applicable, should be applied to these claims as well. The Board should consider that the promoter aspect of claims 59-62 is thus deemed enabled by the specification and the instant rejection should be reversed as to claims 59-62.

VIIC.3. - claims 65- 66

Claims 65 and 66 relate to plasmids comprising the isolated nucleic acids described in claims 6, 43 and 46-53. The Examiner has not set forth any particular explanation of any separate reason for lack of enablement other than those explained above, and therefore the various arguments applied to claims 46-53, as may be applicable, should be applied to these claims as well. The Board should consider that the plasmid aspect of claims 65 and 66 is thus deemed enabled by the specification and the instant rejection should be reversed as to claims 65 and 66.

VIIC.4. - claims 63, 64 and 67-72

Claims 63, 64 and 67-72 relate to transformants and host organisms transformed with chimeric genes or plasmids described in claims 59-63 or 65-66. The Examiner has not set forth any particular explanation of any separate reason for lack of enablement other than those explained above, and therefore the various arguments applied to claims 46-58, as may be applicable, should be applied to these claims as well. The Board should consider that the transformant and host organism aspects of claims 63, 64 and 67-72 are thus deemed enabled by the specification and the instant rejection should be reversed as to claims 63, 64 and 67-72.

VIIC.5. - claim 73

Claim 73 is directed to a method for metabolic modification of a plant using the cloned DNA described in claim 52. The Examiner has not set forth any particular explanation of any separate reason for lack of enablement other than those explained above, and therefore the arguments applied to claim 52, should be applied to this claim as well. The Board should consider that the metabolic transformation aspect of claim 73 is thus deemed enabled by the specification and the instant rejection should be reversed as to claim 73.

VIIC.6. - claim 74

Claim 74 is directed to a method for metabolic modification of a plant using the cloned DNA described in claim 53. The Examiner has not set forth any particular explanation of any separate reason for lack of enablement other than those explained above, and therefore the arguments applied to claim 53, should be applied to this claim as well. The Board should consider that the metabolic transformation aspect of claim 74 is thus deemed enabled by the specification and the instant rejection should be reversed as to claim 74.

VIIC.7. - claim 78

Claim 78 is directed to isolated nucleic acids within claim 52 encoding either the amino acid sequence of SEQ ID NO: 2, which is demonstrated to have RFS activity, or SEQ ID NO: 4, a full length protein sequence having 75% identity to SEQ ID NO: 2 and thus very likely to demonstrate RFS activity. Thus, the breadth of claim 78 encompasses fewer embodiments compared to the scope of claim 52 and the predictability of the art is somewhat higher. Furthermore, the amount of experimentation needed to test operability of a protein of amino acid sequence of SEQ ID NO: 4 is very small and such experimentation is very well guided by the specification; *e.g.* the nucleic acid encoding this amino acid sequence can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 78 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 52, and for these additional reasons.

VIIC.8. - claim 79

Claim 79 is directed to the subset of the chimeric genes of claim 59 in which the portion encoding an amino acid sequence encodes either the amino acid sequence of SEQ ID NO: 2, which is demonstrated to have RFS activity, or SEQ ID NO: 4, a full length protein sequence having 75% identity to SEQ ID NO: 2 and thus very likely to demonstrate RFS activity. Thus, the breadth of claim 79 encompasses fewer embodiments compared to the scope of claim 59 and the predictability of the art is somewhat higher. Furthermore, the amount of experimentation needed to test operability of a protein of amino acid sequence of SEQ ID NO: 4 is very small and such experimentation is very well guided by the specification; *e.g.* the nucleic acid encoding this

amino acid sequence can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 79 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 59, and for these additional reasons.

VIIC.9. - claim 80

Claim 80 is directed to a subset of the plasmids within the scope of claim 65 in which the nucleotide sequence encodes either the amino acid sequence of SEQ ID NO: 2, which is demonstrated to have RFS activity, or SEQ ID NO: 4, a full length protein sequence having 75% identity to SEQ ID NO: 2 and thus very likely to demonstrate RFS activity. Thus, the breadth of claim 80 encompasses fewer embodiments compared to the scope of claim 65 and the predictability of the art is somewhat higher. Furthermore, the amount of experimentation needed to test operability of a protein of amino acid sequence of SEQ ID NO: 4 is very small and such experimentation is very well guided by the specification; *e.g.* the nucleic acid encoding this amino acid sequence can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 80 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 65, and for these additional reasons.

VIIC.10 - claim 81

Claim 81 is directed to methods for metabolic modification of a host organism utilizing a subset of the nucleic acids within the scope of claim 73 in which the nucleotide sequence encodes either the amino acid sequence of SEQ ID NO: 2, which is demonstrated to have RFS activity, or SEQ ID NO: 4, a full length protein sequence having 75% identity to SEQ ID NO: 2 and thus very likely to demonstrate RFS activity. Thus, the breadth of claim 81 encompasses fewer embodiments compared to the scope of claim 73 and the predictability of the art is somewhat higher. Furthermore, the amount of experimentation needed to test operability of a protein of amino acid sequence of SEQ ID NO: 4 is very small and such experimentation is very well guided by the specification; *e.g.* the nucleic acid encoding this amino acid sequence can be

substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 81 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 73, and for these additional reasons.

VIIC.11. - claim 82

Claim 82 is directed to isolated nucleic acids within the scope of claim 53, in which the nucleic acid of the portion encoding an amino acid sequence is obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of these sequences. Thus, the breadth of claim 82 encompasses fewer embodiments compared to the scope of claim 53. Furthermore, the specification examples 5-8 closely describe a species within the scope of claim 82, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 82, is cloned and demonstrated to encode a protein having RFS activity. A second embodiment within claim 82 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS (SEQ ID NO: 4) is cloned using some of the primers recited in claim 82 and a nucleic acid from soybean, which is another leguminous plant. The experimentation required to demonstrate nucleic acids within the scope of claim 82 encode an active RFS is slight, and such experimentation is very well guided by the specification. For example, the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 82 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 53, and for these additional reasons.

VIIC.12. - claim 83

Claim 83 is directed to chimeric genes within the scope of claim 61, in which the nucleic acid of the portion encoding an amino acid sequence is obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of these sequences. Thus, the breadth of claim 83

encompasses fewer embodiments compared to the scope of claim 61. Furthermore, the specification examples 5-8 describe a species within the scope of claim 83, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 83, is cloned and demonstrated to encode a protein having RFS activity. A second embodiment within claim 83 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS is cloned using some of the primers recited in claim 83 and a nucleic acid from soybean, which is another leguminous plant. The experimentation required to demonstrate that nucleic acids within the scope of claim 83 encode an active RFS is slight, and such experimentation is very well guided by the specification. For example, the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 83 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 61, and for these additional reasons.

VIIC.13. - claim 84

Claim 84 is directed to plasmids within the scope of claim 66, in which the nucleic acid of the portion encoding an amino acid sequence is obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of these sequences. Thus, the breadth of claim 84 encompasses fewer embodiments compared to the scope of claim 66. Furthermore, the specification examples 5-8 describe a species within the scope of claim 84, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 84, is cloned and demonstrated to encode a protein having RFS activity. A second embodiment within claim 84 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS (SEQ ID NO: 4) is cloned using some of the primers recited in claim 84 and a nucleic acid from soybean, which is another leguminous plant. The experimentation required to demonstrate a nucleic acid within the scope of claim 84 encodes an active RFS is slight, and such experimentation is very well guided by the specification. For example the nucleic acids within the scope of claim 84 can

be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 84 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 61, and for these additional reasons.

VIIC.14. - claim 85

Claim 85 is directed to a method for metabolic modification within the scope of claim 74, in which nucleic acids are used that are obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of these sequences. Thus, the breadth of claim 85 encompasses fewer embodiments compared to the scope of claim 74. Furthermore, the specification examples 5-8 describe a species within the scope of claim 85, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 85, is cloned and demonstrated to encode a protein having RFS activity. A second embodiment within claim 85 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS is cloned using some of the primers recited in claim 85 and a nucleic acid from soybean, which is another leguminous plant. The experimentation required to demonstrate a nucleic acid within the scope of claim 85 encodes an active RFS is slight, and such experimentation is very well guided by the specification. For example, the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 85 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 74, and for these additional reasons.

VIIC.15. - claim 86

Claim 86 is directed to isolated nucleic acids within the scope of claim 77, in which nucleic acids are used that are obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of these sequences. Thus, the breadth of claim 86 encompasses fewer

embodiments compared to the scope of claim 77. Furthermore, the specification examples 5-8 describe a species within the scope of claim 86, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 86, is cloned and demonstrated to encode a protein having RFS activity. A second embodiment within claim 86 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS is cloned using some of the primers recited in claim 86 and a nucleic acid from soybean, which is another leguminous plant. The experimentation required to demonstrate a nucleic acid within the scope of claim 86 encodes an active RFS is slight, and such experimentation is very well guided by the specification. For example, the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. The rejection of claim 86 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement should be reversed for all of the reasons argued above as to claim 77, and for these additional reasons.

VIID. - Summary and Conclusion

Claims 46-51 stand rejected under 35 U.S.C. § 101, for alleged lack of utility of the claimed invention. The Examiner's position is that the specification fails to set forth any well-established or otherwise substantial utility for the claimed invention.

The Examiner relies upon an allegation that one of ordinary skill in the art, at the time the present application was filed, was not able to sufficiently distinguish a nucleic acid encoding a raffinose synthase enzyme from a nucleic acid encoding a stachyose synthase enzyme. Therefore, the utility of a nucleic acid within the sequences in claims 46-51 is not established, because the skilled artisan is uncertain whether the nucleic acid in hand is used in the manner of a raffinose synthase or in the manner of a stachyose synthase.

Appellants submit that this argument is not persuasive. The present record contains substantial evidence in support of Appellants' assertion of utility of the invention. In particular, the Nagasawa Declaration attached to Appellants' paper of September 12, 2005 firmly establishes that molecular phylogenetic analysis utilizing the sequence data from the

specification identifies amino acid sequences obtained from the working examples as being raffinose synthases. The analysis presented in the Nagasawa Declaration is of a kind accepted by one of ordinary skill in the art as sufficient to support at least a hypothesis of similar biological activity.[3] That is, such analysis establishes the likelihood by the preponderance of the evidence that the proteins of the instant application are indeed raffinose synthases.

It seems that the Examiner is mistakenly applying a much higher burden of proof to the issue. Such is legal error that compels reversal of the Examiner's decision that the invention of claims 46-51 lack utility. Accordingly, the rejection of claims 46-51 under 35 U.S.C. § 101 for alleged lack of utility must be reversed.

Claims 48-77 and 82-86 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description of the invention. The Examiner's argument on this issue is that the specification fails to describe any particular amino acid sequence that defines a protein as having raffinose synthase activity, and therefore the generic invention is not described.

Appellants submit that this argument is not persuasive either. In the first instance, the specification asserts that the defined sequences in SEQ ID NOS: 1-8 define nucleic acids according to the invention, either at the nucleic acid or at the amino acid level. Appellants submit that specific description of a structure constitutes substantial evidence that they "possess" the invention so described and have placed such an invention in the hands of the public. *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991).

Furthermore, the specification describes a number of PCR primers, derived from the data of SEQ ID NOs: 2, 4, 6 and 8, that are useful when applied to template nucleic acids from plant types associated with the primer sequences as described in the specification, to obtain further cloned cDNAs encoding raffinose synthase enzymes. The specification also describes how to test any nucleic acids obtained by such a technique for activity of a raffinose synthase. Therefore, the invention is at the very least well-described in "product-by-process" terms. *Fiers*

[3] This assertion is supported by use of a similar analysis in a paper, Richmond et al. (2000), cited by the Examiner in

v. Revel, 25 USPQ2d at 1605. One may also consider that the PCR primers represent minimal nucleotide sequences that must be present to define a nucleic acid as one encoding a raffinose synthase. Therefore, to this degree at least, a "structure-function" relationship is described in the specification.

Thus, Appellants submit that the specification meets the legal standard, *i.e.* it evidences that the inventors were in possession of the invention as claimed, for adequate written description of the claimed invention. Accordingly, the rejection of claims 48-77 and 82-86 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support, should be reversed.

Finally, claims 46-86 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner's position is essentially that, since one of ordinary skill in the art is unable to distinguish a nucleic acid encoding a raffinose synthase enzyme from a nucleic acid encoding a stachyose synthase enzyme, the specification fails to teach the skilled artisan how to use the present invention.

This rejection fails in the first instance because the Examiner fails to establish any *prima facie* lack of enablement. Proper consideration of the question of enablement requires establishing that undue experimentation is required to practice the full scope of the invention. This question is addressed by considering a number of factors. *In re Wands*, 8 USPQ2d at 1400.

However, the Examiner's explanation of the rejection addresses only the question of whether one of ordinary skill in the art, having a particular nucleic acid in hand, can predict, based upon its sequence, whether or not that nucleic acid encodes a raffinose synthase enzyme, or whether instead it encodes a stachyose synthase. Such analysis ignores the other factors to be considered.

On the other hand, Appellants explain that the specification is enabling of the claimed invention, addressing the remaining considerations required under *Wands*, and also present

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an effort to demonstrate lack of enablement.

evidence to support an allegation that the skilled artisan, using the teachings of the specification in a manner accepted in the art at the time the invention was made (*e.g.* molecular phylogeny based upon degree of amino acid sequence similarity) can easily distinguish a raffinose synthase enzyme from a stachyose synthase enzyme. Appellants also point out that the specification provides express guidance, in the form of a working example, of how to determine biochemically if a protein expressed from a cloned nucleic acid exhibits activity of a raffinose synthase. Therefore it is plainly established that the present specification is enabling of the claimed invention and so the rejection of claims 46-86 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, must be reversed.

The favorable action of reversal of all of the rejection of claims 46-51 under 35 U.S.C. § 101 for alleged lack of utility, the rejection of claims 48-77 and 82-86 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support and of claims 46-77 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement, and remand to the Examiner for allowance of all of the pending claims, is respectfully requested.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A include the amendments filed by Applicant on September 12, 2005.

IX. EVIDENCE

A copy of evidence pursuant to §§ 1.130, 1.131, or 1.132 and/or evidence entered by or relied upon by the examiner that is relevant to this appeal is attached hereto as Appendix B.

1. Tables 1 and 3, which were presented attached to Appellants' paper of November 15, 2004.

2. Table 2, presented attached to Appellants' paper of February 24, 2004

3. Exhibit 1, explanation of various sequence analysis programs, attached to Appellants' paper of November 15, 2004.

4. Exhibit 4, Lehle and Tanner, *Eur. J. Biochem.* 38:103-110 (1973), attached to Appellants' paper of November 15, 2004.

5. Declaration of Akistu NAGASAWA, attached to Appellants' paper of September 12, 2005.

6. Richmond et al., *Plant Physiol.* 124:495-498 (2000), cited by the Examiner in Office Action of March 11, 2005.

7. Duggleby, *Gene* 190:245-249 (1997), cited by the Examiner in Office Action of March 11, 2005.

8. Peterbauer et al., *Planta* 215:839-846 (2002), cited by the Examiner in Office Action of March 11, 2005.

X. RELATED PROCEEDINGS

There are no prior decisions of any Court or of the Board of Appeals and Interferences in this matter.

Dated: December 26, 2006

Respectfully submitted,

By _____

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 08/992,914

The pending claims 46-86, set forth below, are on appeal:

46. (Previously presented) An isolated nucleic acid comprising a nucleotide sequence coding for the amino acid sequence of SEQ ID NO:4.

47. (Previously presented) The isolated nucleic acid of claim 46 wherein the nucleotide sequence is that of SEQ ID NO:3.

48. (Previously presented) An isolated nucleic acid comprising a nucleotide sequence coding for the amino acid sequence of SEQ ID NO:6.

49. (Previously presented) The isolated nucleic acid according to claim 48, wherein the nucleotide sequence is the sequence of SEQ ID NO:5.

50. (Previously presented) An isolated nucleic acid comprising a nucleotide sequence coding for the amino acid sequence of SEQ ID NO: 8.

51. (Previously presented) The isolated nucleic acid according to claim 50, wherein the nucleotide sequence is the sequence of SEQ ID NO: 7.

52. (Currently amended) An isolated nucleic acid comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence of SEQ ID NO:1,

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:2,

(c) a nucleotide sequence of SEQ ID NO:3,

(d) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:4,

(e) a nucleotide sequence of SEQ ID NO:5,

(f) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:6,

(g) a nucleotide sequence of SEQ ID NO:7, and

(h) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:8.

53. (Currently amended) A nucleic acid isolated from a plant comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9, SEQ ID NO:15, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and SEQ ID NO:58 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, and SEQ ID NO:53, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12, SEQ ID NO:19, SEQ ID NO:65, and SEQ ID NO:68 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:21, and SEQ ID NO:70, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(c) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a lamiaceous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:71 and SEQ ID NO:73 and a PCR primer selected from the group consisting of SEQ ID NO:72 and SEQ

ID NO:74, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:5 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(d) a nucleotide sequence obtained by amplifying via the RACE process a nucleic acid obtained from a monocotyledonous plant with a PCR primer selected from the group consisting of SEQ ID NO:77 and SEQ ID NO:78, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:7 in 0.9 M NaCl, 0.09 M citric acid at 65°C.

54. (Previously presented) The isolated nucleic acid (a) according to claim 53, wherein the leguminous plant is broad bean.

55. (Previously presented) The isolated nucleic acid (b) according to claim 53, wherein the leguminous plant is soybean.

56. (Previously presented) The isolated nucleic acid (c) according to claim 53, wherein the lamiaceous plant is Japanese artichoke.

57. (Previously presented) The isolated nucleic acid (d) according to claim 53, wherein the monocotyledonous plant is a gramineous plant.

58. (Previously presented) The isolated nucleic acid according to claim 57, wherein the gramineous plant is corn.

59. (Previously presented) A chimeric gene comprising a nucleic acid comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence of SEQ ID NO:1,

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:2,

(c) a nucleotide sequence of SEQ ID NO:3,

(d) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:4,

(e) a nucleotide sequence of SEQ ID NO:5,

(f) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:6,

(g) a nucleotide sequence of SEQ ID NO:7, and

(h) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:8;

and a promoter operatively linked thereto.

60. (Previously presented) The chimeric gene of claim 59, in which the promoter is selected from the group consisting of a promoter functional in *E. coli*, a yeast alcohol dehydrogenase promoter, an adenovirus major late promoter, an SV40 early promoter, a baculovirus promoter, a nopaline synthase promoter, an octopine synthase promoter, a cauliflower mosaic virus 19S promoter, a cauliflower mosaic virus 35S promoter, a phenylalanine-amino lyase promoter, a chalcone synthase promoter, a glycinin promoter and a pathogenesis-related protein promoter.

61. (Previously presented) A chimeric gene comprising a nucleic acid isolated from a plant comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9, SEQ ID NO:15, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and SEQ ID NO:58 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, and SEQ ID NO:53, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12, SEQ ID NO:19, SEQ ID NO:65, and SEQ ID NO:68 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:21, and SEQ ID NO:70, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(c) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a lamiaceous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:71 and SEQ ID NO:73 and a PCR primer selected from the group consisting of SEQ ID NO:72 and SEQ ID NO:74, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:5 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(d) a nucleotide sequence obtained by amplifying via the RACE process a nucleic acid obtained from a monocotyledonous plant with a PCR primer selected from the group consisting of SEQ ID NO:77 and SEQ ID NO:78, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:7 in 0.9 M NaCl, 0.09 M citric acid at 65°C;

and a promoter operatively linked thereto.

62. (Previously presented) The chimeric gene of claim 61, in which the promoter is selected from the group consisting of a promoter functional in *E. coli*, a yeast alcohol dehydrogenase promoter, an adenovirus major late promoter, an SV40 early promoter, a baculovirus promoter, a nopaline synthase promoter, an octopine synthase promoter, a cauliflower mosaic virus 19S promoter, a cauliflower mosaic virus 35S promoter, a phenylalanine-amino lyase promoter, a chalcone synthase promoter, a glycinin promoter and a pathogenesis-related protein promoter.

63. (Previously presented) A transformant obtained by introducing the chimeric gene of claim 59 into a host organism.

64. (Previously presented) A transformant obtained by introducing the chimeric gene of claim 61 into a host organism.

65. (Previously presented) A plasmid comprising a nucleic acid comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence of SEQ ID NO:1,

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:2,

(c) a nucleotide sequence of SEQ ID NO:3,

(d) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:4,

(e) a nucleotide sequence of SEQ ID NO:5,

(f) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:6,

(g) a nucleotide sequence of SEQ ID NO:7, and

(h) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:8.

66. (Previously presented) A plasmid comprising a nucleic acid isolated from a plant comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9, SEQ ID NO:15, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and SEQ ID NO:58 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, and SEQ ID NO:53, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12, SEQ ID NO:19, SEQ ID NO:65, and SEQ ID NO:68 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:21, and SEQ ID NO:70, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(c) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a lamiaceous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:71 and SEQ ID NO:73 and a PCR primer selected from the group consisting of SEQ ID NO:72 and SEQ ID NO:74, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:5 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(d) a nucleotide sequence obtained by amplifying via the RACE process a nucleic acid obtained from a monocotyledonous plant with a PCR primer selected from the group consisting of SEQ ID NO:77 and SEQ ID NO:78, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:7 in 0.9 M NaCl, 0.09 M citric acid at 65°C.

67. (Previously presented) A host organism transformed with the plasmid of claim 65, or a cell thereof.

68. (Previously presented) The host organism of claim 67 that is a microorganism.

69. (Previously presented) A plant transformed with the plasmid of claim 65, or a cell thereof.

70. (Previously presented) A host organism transformed with the plasmid of claim 66, or a cell thereof.

71. (Previously presented) The host organism of claim 70 that is a microorganism.

72. (Previously presented) A plant transformed with the plasmid of claim 66, or a cell thereof.

73. (Previously presented) A method for metabolic modification, which comprises introducing a nucleic acid comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an α(1→6) bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence of SEQ ID NO:1,

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:2,

(c) a nucleotide sequence of SEQ ID NO:3,

(d) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:4,

(e) a nucleotide sequence of SEQ ID NO:5,

(f) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:6,

(g) a nucleotide sequence of SEQ ID NO:7, and

(h) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:8,

into a host organism or a cell thereof, so that the content of raffinose family oligosaccharides in the host organism or the cell thereof is changed.

74. (Previously presented) A method for metabolic modification, which comprises introducing a nucleic acid isolated from a plant comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an α(1→6) bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9, SEQ ID NO:15, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and SEQ ID NO:58 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, SEQ ID

NO:17, and SEQ ID NO:53, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12, SEQ ID NO:19, SEQ ID NO:65, and SEQ ID NO:68 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:21, and SEQ ID NO:70, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(c) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a lamiaceous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:71 and SEQ ID NO:73 and a PCR primer selected from the group consisting of SEQ ID NO:72 and SEQ ID NO:74, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:5 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(d) a nucleotide sequence obtained by amplifying via the RACE process from a nucleic acid obtained from a monocotyledon with a PCR primer selected from the group consisting of SEQ ID NO:77 and SEQ ID NO:78, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:7 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

into a host organism or a cell thereof, so that the content of raffinose family oligosaccharides in the host organism or the cell thereof is changed.

75. (Previously presented) An isolated nucleic acid comprising (i) a polynucleotide having a sequence that encodes a protein having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, or 8 or (ii) a polynucleotide having a sequence complementary to said sequence.

76. (Previously presented) An isolated nucleic acid comprising (i) a polynucleotide having a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, or 7 or (ii) a polynucleotide having a sequence complementary to said sequence.

77. (Previously presented) A nucleic acid isolated from a plant comprising a nucleotide sequence coding for an amino acid sequence of a protein which produces raffinose by combining a D-galactosyl group through an $\alpha(1\rightarrow6)$ bond with a hydroxyl group attached to the carbon atom at position 6 of a D-glucose residue in a sucrose molecule, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence obtained by amplifying a nucleic acid obtained from broad bean with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9, SEQ ID NO:15, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and SEQ ID NO:58 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, and SEQ ID NO:53, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from soybean with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12, SEQ ID NO:19, SEQ ID NO:65, and SEQ ID NO:68 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:21, and SEQ ID NO:70, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C,

(c) a nucleotide sequence obtained by amplifying a nucleic acid obtained from Japanese artichoke with a combination of a PCR primer selected from the group consisting of SEQ ID NO:71 and SEQ ID NO:73 and a PCR primer selected from the group consisting of SEQ ID NO:72 and SEQ ID NO:74, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:5, in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(d) a nucleotide sequence obtained by amplifying via the RACE process from a nucleic acid obtained from corn with a PCR primer selected from the group consisting of SEQ ID NO:77 and SEQ ID NO:78, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:7 in 0.9 M NaCl, 0.09 M citric acid at 65°C.

78. (Previously presented) The nucleic acid according to claim 52, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence of SEQ ID NO:1,

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:2,

(c) a nucleotide sequence of SEQ ID NO:3, and

(d) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:4.

79. (Previously presented) The chimeric gene according to claim 59, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence of SEQ ID NO:1,

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:2,

(c) a nucleotide sequence of SEQ ID NO:3, and

(d) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:4.

80. (Previously presented) The plasmid according to claim 65, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence of SEQ ID NO: 1,

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:2,

(c) a nucleotide sequence of SEQ ID NO:3, and

(d) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO;4.

81. (Previously presented) The method for metabolic modification according to claim 73, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence of SEQ ID NO:1,

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:2,

(c) a nucleotide sequence of SEQ ID NO:3, and

(d) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:4.

82. (Previously presented) The isolated nucleic acid according to claim 53, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9 and SEQ ID NO:15 and a PCR primer selected from the group consisting of SEQ ID NO: 10, SEQ ID NO:11, and SEQ ID NO:17, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO: 12 and SEQ ID NO:19 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:21, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C.

83. (Previously presented) The chimeric gene according to claim 61, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9 and SEQ ID NO:15 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:17, wherein said nucleotide sequence hybridizes with a

nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12 and SEQ ID NO:19 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:21, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C.

84. (Previously presented) The plasmid according to claim 66, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide. sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9 and SEQ ID NO:15 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:17, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12 and SEQ ID NO:19 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:21, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C.

85. (Previously presented) The method for metabolic modification according to claim 74, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ

ID NO:9 and SEQ ID NO:15 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:17, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from a leguminous plant with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12 and SEQ ID NO:19 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:21, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 0.09 M citric acid at 65°C.

86. (Previously presented) The isolated nucleic acid according to claim 77, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence obtained by amplifying a nucleic acid obtained from broad bean with a combination of a PCR primer selected from the group consisting of SEQ ID NO:9 and SEQ ID NO:15 and a PCR primer selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:17, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:1 in 0.9 M NaCl, 0.09 M citric acid at 65°C, and

(b) a nucleotide sequence obtained by amplifying a nucleic acid obtained from soybean with a combination of a PCR primer selected from the group consisting of SEQ ID NO:12 and SEQ ID NO:19 and a PCR primer selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:21, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of SEQ ID NO:3 in 0.9 M NaCl, 4.09 M citric acid at 65°C.

APPENDIX B

The following items are of record as evidence in the present application and are attached hereto in support of Appellants' Appeal Brief:

1. Tables 1 and 3, which were presented attached to Appellants' paper of November 15, 2004.

2. Table 2, presented attached to Appellants' paper of February 24, 2004

3. Exhibit 1, explanation of various sequence analysis programs, attached to Appellants' paper of November 15, 2004.

4. Exhibit 4, Lehle and Tanner, *Eur. J. Biochem.* 38:103-110 (1973), attached to Appellants' paper of November 15, 2004.

5. Declaration of Akistu NAGASAWA, attached to Appellants' paper of September 12, 2005.

6. Richmond et al., *Plant Physiol.* 124:495-498 (2000), cited by the Examiner in Office Action of March 11, 2005.

7. Duggleby, *Gene* 190:245-249 (1997), cited by the Examiner in Office Action of March 11, 2005.

8. Peterbauer et al., *Planta* 215:839-846 (2002), cited by the Examiner in Office Action of March 11, 2005.